



# controversial topics in surgery

## Prostate cancer treatment

The treatment of localised prostate cancer remains controversial since there is no clear evidence of the superiority of any one treatment modality over any other. However, evidence is emerging that, in some patient groups, radical treatment may confer a survival advantage. The issue, therefore, appears to be one of treatment efficacy against complications and effects on quality of life.

Compared to watchful waiting, radical prostatectomy remains the only treatment modality where there is published evidence of a survival advantage. Goldstraw and Kirby, therefore, argue that surgery remains the gold standard treatment despite its slightly higher complication rates compared to external beam radiotherapy. Langley, however, demonstrates that brachytherapy now offers effective treatment of prostate cancer with oncological outcomes which are certainly comparable with those of surgery and he describes a lower risk of complications. Whether the complication

rates are really more acceptable is perhaps less clear than he suggests since there is a danger in comparing figures from acknowledged centres of excellence with those from units performing much lesser numbers of procedures.

In considering new treatment modalities, healthcare systems have now become obliged to consider costs. Hitherto, new technologies including brachytherapy and laparoscopic or robotic techniques have proved expensive compared to traditional surgery. It is perhaps difficult, therefore, to see the NHS wishing to continue funding for procedures where an acceptable, cheaper alternative exists.

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## The case for radical prostatectomy

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The management of clinically localised prostate cancer is controversial. Walsh and Donker<sup>1</sup> first described the anatomical basis for nerve-sparing radical prostatectomy in 1982 and this is considered by many to be the 'gold standard' treatment. However, other strategies exist including watchful waiting, external beam radiotherapy and brachytherapy. Which of these modalities is the optimal treatment is fiercely debated and there is only a scanty evidence base available with no large-scale, randomised trials of radical prostatectomy versus radiotherapy or brachytherapy.

### *Surgery versus watchful waiting*

The most significant report comparing surgery with watchful waiting was produced by Bill-Axelsson *et al.*<sup>2</sup> in

2005. They reported the final results from the Scandinavian prostate cancer group study – a randomised, prospective study following nearly 700 men with early (moderately- and well-differentiated) prostate cancer over a 10-year period (1989–1999). Importantly, this is the only report to show a survival benefit with any singular modality treatment. During a median period of 8.2 years, death due to prostate cancer occurred in 14.4% of men assigned to watchful waiting versus 8.6% in the surgery group. Table 1 shows that the difference in the cumulative incidence of death due to prostate cancer increases from 2.0% after 5 years to 5.3% after 10 years, for a relative risk of 0.56. Admittedly these may be small benefits but, more significantly, results showed a considerable reduction in metastatic disease of 1.7% to 10.2% at 5 years and 10 years, respectively. Because

**Table 1** Cumulative incidence of the main end-points and corresponding relative risks

End-point	Cumulative incidence				Absolute risk reduction (95% CI)	RR (95% CI)	P-value
	Radical-prostatectomy group		Watchful-waiting group				
	Total no.	%(95% CI)	Total no.	%(95% CI)			
Disease-specific mortality							
At 5 years	30	2.3 (1.2–4.6)	50	4.3 (2.6–7.1)	2.0 (–0.6 to 4.7)		
At 10 years	30	9.6 (6.5–14.2)	50	14.9 (11.2–19.8)	5.3 (–0.3 to 11.0)	0.56 (0.36–0.88)	0.01
Distant metastases							
At 5 years	50	8.1 (5.7–11.6)	79	9.8 (7.1–13.5)	1.7 (–2.5 to 6.0)		
At 10 years	50	15.2 (11.4–20.3)	79	25.4 (20.4–31.5)	10.2 (3.1–17.2)	0.60 (0.42–0.86)	0.004

Taken from the data of Bill-Axelson *et al.*<sup>2</sup> The absolute risk reduction and relative risks are for radical prostatectomy as compared with watchful waiting. RR denotes relative risk and CI confidence interval.

clinical manifestations of disseminated disease virtually always precede death, this finding may herald a further lowering of the risk of death due to prostate cancer in the radical prostatectomy group after a longer period of follow-up.<sup>2</sup>

One point of note is that subgroup analysis revealed that the reduction in disease-specific mortality was greatest among, or even limited to, patients younger than 65 years. Although the study was not powered to analyse subgroups, some may argue about the benefit of older patients undergoing surgery. As a consequence, in most cases, radical prostatectomy should only be undertaken in those with an expected life-expectancy of  $\geq 10$ -years.

#### *Surgery versus radiotherapy*

It is probably unrealistic now to expect a well-designed, prospective randomised study with long-term follow-up to be undertaken comparing surgery with radiotherapy. Furthermore, the studies that do exist are hampered by differences in case selection, short duration of follow-up and varying definitions of biochemical failure. One benefit of surgery is the ability to sample lymph nodes intra-operatively. Traditionally, if frozen section is performed and proves to be positive, the radical surgery is immediately abandoned. This automatically places the surgical arm of studies at an advantage compared to radiotherapy as this patient group has effectively been down-staged. Paulson *et al.*<sup>5</sup> performed the only randomised study of surgery versus radiotherapy and this demonstrated improved surgical survival outcomes. This study was never widely accepted as it was set in 1982, in the pre-prostate specific antigen (PSA) era, and the relevance to contemporary practice

is unclear. However, several large retrospective studies exist: D'Amico *et al.*<sup>4</sup> performed analysis of over 2600 men with early prostate cancer and results supported a survival advantage in those treated with surgery. This study is also controversial and it has been pointed out that only 380 men were treated in the radiotherapy arm and conventional dose radiation was used (69–71 Gy). Higher dose conformal or intensity-modulated techniques are now being used and do improve results. Lu-Yao *et al.*<sup>5</sup> performed the largest study to date using the surveillance, epidemiology, and end results (SEER) data of the National Cancer Institute. In an intention-to-treat analysis, the 10-year disease-specific survival was better for surgery compared with radiation in patients with well, moderately, and poorly differentiated disease. This is interesting as by using the intention-to-treat approach, the confounding factor of lymph node sampling and down-staging is taken into account. Admittedly, not all comparative studies find in favour of surgery and Martinez *et al.*<sup>6</sup> reported no significant survival difference between radiotherapy and surgery groups but this involved a relatively small study group (382 patients) and a short median follow-up of 5.5 years.

#### *Quality of life issues*

Overall, the available evidence is in favour of a moderate survival advantage with surgery compared to radiotherapy. However, surgery may have significant morbidity, especially in terms of erectile dysfunction and incontinence. With the increasingly young age of patients undergoing radical prostate surgery, this potentially has a great impact on quality of life (QoL) issues. Comparative studies on QoL issues



**Figure 1** The Da Vinci robot (Intuitive Surgical™). The device consists of a master console (left) and a slave system (right) controlling 3 or 4 telerobotic arms. Photo courtesy of Intuitive Surgical (Sunnyvale, CA, USA).

suggest that surgery has a higher rate of urinary incontinence compared to radiotherapy, 8% versus 1%, respectively. Both treatment modalities do result in impaired sexual function, but overall sexual function (interest, frequency, bothersome) is similar between the two groups.<sup>7</sup> However, reported erectile dysfunction is more prevalent in the surgery group at 79.3% versus 63.5% at 5 years. Conversely, radiotherapy does result in more bowel-related problems mainly tenesmus, urgency and rectal bleeding.

#### *The future*

Continual refinements to the nerve-sparing prostatectomy are being made and potency rates continue to improve. Catalona *et al.*<sup>8</sup> reported potency rates approaching 70% with bilateral nerve sparing surgery. Recently, the Vattikuti Institute (Detroit, MI, USA) has pioneered the development of the Robotic Radical Prostatectomy (RRP) using the Da Vinci robot (Intuitive surgical™).<sup>9</sup> This technology allows three-dimensional stereoscopic vision with x10 magnification, increased dexterity and reduction of surgical tremor (Fig. 1). While this system shows similar oncological efficacy, reported benefits include reduced blood loss, decreased pain and reduced hospital stay. Theoretically, the enhanced visualisation of the neurovascular bundles at the time of RRP might be expected to result in improved erectile function. In December 2005, Menon *et al.*<sup>10</sup> published 1-year follow-up of patients undergoing robotic radical prostatectomy (prostate fascia-sparing). These results revealed that an impressive

86% of men were potent with the use of phosphodiesterase 5 inhibitors.<sup>10</sup>

#### *Conclusions*

Radical prostatectomy remains the gold-standard treatment for clinically localised prostate cancer. Cumulative data suggest that it has a survival advantage over radiotherapy, but it is troubled by surgical morbidity especially erectile dysfunction and incontinence. Recent surgical advances, particularly with robotic radical prostatectomy, have shown encouraging results with minimised associated morbidity and maximised quality of life while still achieving surgical cure.

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## Permanent low-dose rate prostate brachytherapy

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Given the significant side-effects of incontinence and impotence with radical prostatectomy, an oncological operation with a reported positive margin rate of up to 30–40%,<sup>1</sup> for a disease that for many will not be fatal if untreated,<sup>2</sup> it is unfortunate that not all patients are suitable for prostate brachytherapy. Prostate brachytherapy has been shown to be a highly effective curative treatment for early prostate cancer with outcome results stretching to 13 years and meta-analysis studies revealing that it is just as effective in curing prostate cancer as surgery yet with a fraction of the side effects. This article will substantiate these claims.

### Brachytherapy procedure

Prostate brachytherapy involves the implantation of tiny radioactive seeds transperineally into the prostate gland (Fig. 1). The procedure takes 30–45 min to perform and may be delivered as a day-case. Initially, patients undergo a planning scan where detailed transrectal ultrasound images of the prostate are obtained. These images are used to produce a three dimensional model of the prostate from which the precise number and position of the seeds are determined. The seeds are then implanted into the prostate gland under a general anaesthetic transperineally using transrectal ultrasonography to guide the needles carrying the seeds to their pre-planned position.

Brachytherapy offers patients the ultimate in conformal radiotherapy with the radiation sources implanted in real-time into the cancerous gland; as the radiation is emitted from a point source, the surrounding tissues can be better spared. The minimum prescribed dose to the prostate gland is 145 Gy using Iodine-125 implants with about 50% of the gland receiving 150% of the dose (*i.e.* 217 Gy; see Fig. 2). Such doses of radiation have a biological equivalence much greater than that which can be delivered by any of the external beam techniques, including IMRT. In cases where

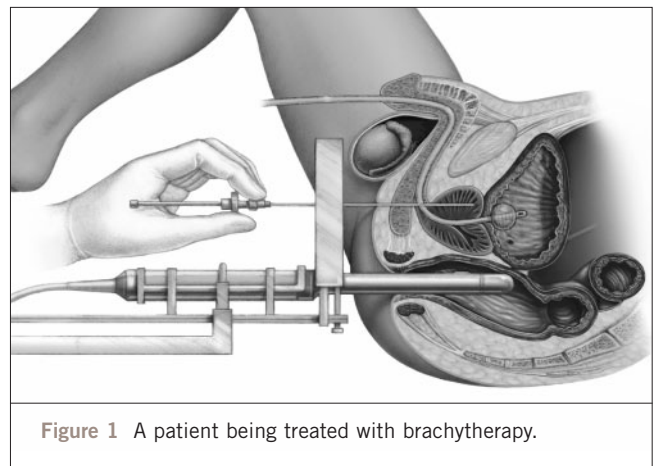
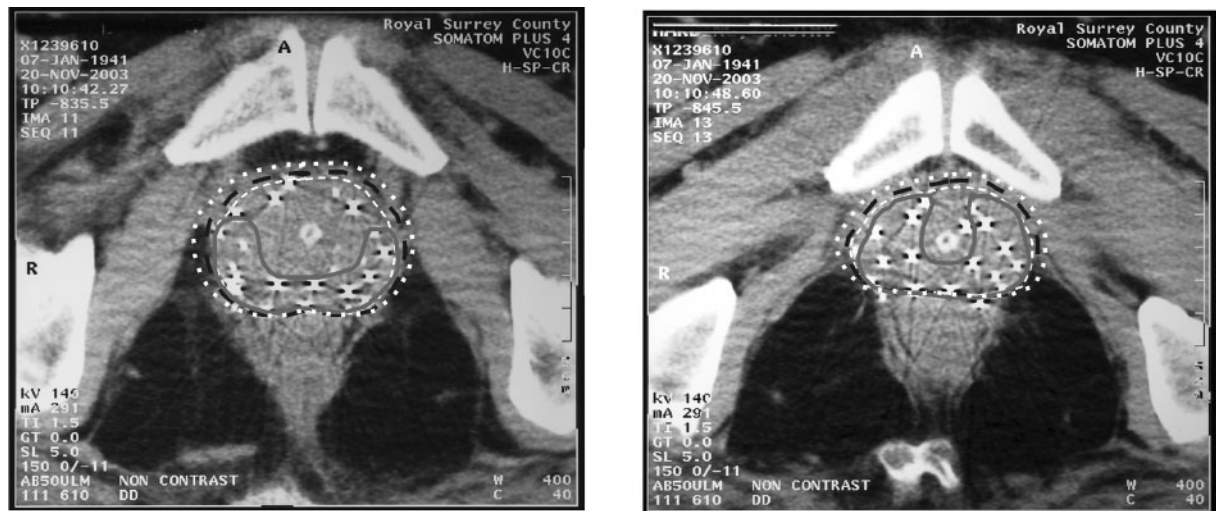


Figure 1 A patient being treated with brachytherapy.

there is an increased chance of local extension of the prostate cancer, a combined treatment using 45 Gy external beam radiation to the whole pelvis followed by a 110 Gy brachytherapy implant has been used with good effect.

### Brachytherapy results

In 1988, the first 10-year results of transperineal ultrasound guided prostate brachytherapy were published from Seattle, USA. Examining their overall series of 634 patients, 402 treated with an implant alone (Iodine-125/Palladium-105) and 232 treated by an implant and external beam radiation reveals a progression-free survival rate of 77%.<sup>3</sup> When stratified by risk factors (Table 1), low-, intermediate- and high-risk disease had progression-free survival rates of 87%, 74% and 45% respectively. Similar 10-year results have been recently reported by others with prostate specific antigen (PSA)-free survival rates of 79% from a cohort of 883 patients<sup>4</sup> and results on 619 patients at 13 years continue to show a PSA-free survival of 77%.<sup>5</sup>



**Figure 2** Post-implant CT scan taken with the patient catheterised at mid gland and apical levels of the prostate. The Iodine-125 sources are clearly seen within the prostate tissue. The dashed white line shows the periphery of the prostate. The dashed black isodose line is a simulation showing coverage of the prescribed radiation dose, 145 Gy. The grey continuous isodose line simulates that portion of the prostate receiving 150% of the prescription dose, 217 Gy. The dotted white isodose line simulates the 72 Gy isodose showing the rapid fall off in radiation to the surrounding structures.

The 10-year, disease-specific survival rates for 1561 men treated by brachytherapy, with or without EBRT and hormone therapy, have recently been published with a 96% survival, suggesting that the excellent results obtained using PSA as a surrogate marker appear to translate to actual clinical outcomes.<sup>6</sup> The durability of brachytherapy has been demonstrated in 10- and 12-year results from Seattle. No further recurrences were identified in patients who were deemed biochemical free at 12 years compared to 10 years of follow-up.<sup>7</sup>

#### *Reproducibility of brachytherapy results*

The results achieved in the US appear exportable to the UK. In Guildford, UK, we have treated over 800 patients and prospectively assessed outcomes of both PSA-free survival using the ASTRO criteria as well as continence, potency and quality of life parameters using validated questionnaires.

The results of our first 300 patients treated with median follow-up of 45 months (range, 33–82 months) show an overall actuarial PSA-free survival of 93% at 5 years.<sup>8</sup>

Stratified by risk group, the actuarial survivals were 96%, 89% and 93% for low-, intermediate- and high-risk disease, respectively. There was no statistical difference in survival between hormone naive patients and those treated with 3 months neo-adjuvant therapy, (95% versus 93%,  $P = 0.3$ , respectively).

#### *Comparison results*

There are currently no randomised studies comparing brachytherapy to radical prostatectomy. In a study of over 6500 patients treated with brachytherapy, radiotherapy or radical prostatectomy, who were stratified according to a PSA and Gleason score, there was no significant difference between any of the primary treatment options in PSA-free survivals.<sup>9</sup> Other, further, retrospective studies of 1305 and 2991 have also failed to demonstrate any clear superiority of one treatment over the other.<sup>10</sup>

#### *Complications*

Incontinence is rare, occurring in < 1% in our most contemporary series<sup>11</sup> by comparison to radical prostatectomy series with rates as high as 27%.<sup>12</sup>

**Table 1** Risk group classification of prostate cancer patients

Risk group	PSA	Stage	Gleason grade
Low	≤ 10	T1a–T2b	2–6
Intermediate (1 factor present)	> 10	≥ T2c	≥ 7
High (2 or more factors present)	> 10	≥ T2c	≥ 7



Erectile dysfunction seems significantly less common than with radical prostatectomy; impotence from UK and European studies is as high as 80% despite nerve-sparing techniques.<sup>13</sup> Potters *et al.*<sup>14</sup> reported on the potency of 482 patients pre-treatment and revealed a potency rate of 90% in men younger than 60 years treated with an implant alone. In our prospective study at Guildford, we have a 67% potency rate at 1 year in patients with an IIEF score  $\geq 11/25$ , who were potent pre-treatment. A meta-analysis comparing erectile function outcomes reveals a 76% chance of remaining potent when treated by brachytherapy (reducing to 60% with combination therapy) compared to 34% after a nerve-sparing radical prostatectomy and 25% after a standard radical prostatectomy.<sup>15</sup>

Proctitis is relatively uncommon, occurring in about 5% of cases and, in our experience, has always resolved with conservative medication alone.<sup>8</sup>

The primary complication of prostate brachytherapy is a temporary deterioration of urinary function with increased irritative and obstructive symptoms. Patients are routinely treated with  $\alpha$ -blockers. We have found that such urinary symptoms assessed by the IPSS are improved at 3 months and return to base line by 9 months.<sup>11</sup> Temporary urinary retention can occur, usually for only 2–3 weeks; with careful case selection, the risk can be minimised to 5% or less.<sup>8,11</sup>

It is this temporary deterioration in urinary symptoms that limits the use of prostate brachytherapy. Patients with large prostate glands (+ 75 cc), poor urinary flow rates with moderate-to-severe urinary symptoms (IPSS < 15) and an inability to empty their bladder completely have exaggerated post-implant symptoms and, in the opinion of the author, are often best served by a laparoscopic radical prostatectomy so removing the obstructing gland as well as treating the cancer. However, with increasing awareness that early prostate cancer is normally a symptom-less disease and with the rise in PSA screening in the UK, the majority of patients with early prostate cancer are suitable for prostate brachytherapy.

### Summary

Brachytherapy is highly effective in the treatment of localised prostate cancer and results from the US have been reproduced in the UK. A recent review article in *The Lancet* discussing the clinical decision-making aspects of the treatment of early prostate cancer, highlighted the relatively low risk of urinary incontinence, rectal complications and sexual dysfunction following brachytherapy compared to radical prostatectomy.<sup>16</sup> With many patients treated by brachytherapy in a day-case setting and being able to return to work within a few days, the advantages of brachytherapy are readily apparent. However, as with every treatment in

medicine, case selection is critical to ensure satisfied patients with a low morbidity and high chance of cure.

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